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STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 NEW YORK AVENUE, N.W.
WASHINGTON, DC 20005

EXAMINER	
EPPERSON, JON D	

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/987,456
Filing Date: November 14, 2001
Appellant(s): ZAUDERER ET AL.

Tracy L. Muller
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 7/6/07 appealing from the Office action mailed 10/31/06

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of claims

The statement of the status of claims contained in the brief is correct.

(4) Status of amendments

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of claimed subject

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of rejection to be reviewed on appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence relied on

WO 93/01296	Rowlands et al.	01-1993
WO 00/28016	Zauderer et al.	05-2000

Waterhouse et al., "Combinatorial infection and in vivo recombination: a strategy for making large phage antibody repertoires" Nucleic Acids Research, vol. 21, no. 9 (1993), pp. 2265-2266.

(9) Grounds of rejection

Claim Rejections - 35 USC § 103

Claims 84, 88-97, 99, 103, 107-122 and 127-131 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rowlands et al. (WO 93/01296) (Date of Patent is **January 21, 1993**) and Zauderer et al. (WO 00/28016) (Date of Patent is **May 18, 2000**) and Waterhouse et al. (Waterhouse, P.; Griffiths, A.D.; Johnson, K.S.; Winger, G. "Combinatorial infection and in vivo recombination: a strategy for making large phage antibody repertoires" *Nucleic Acids Research*, **1993**, 21, 9, 2265-2266).

For ***claims 84, 88, 96-97, 113, 117***, Rowlands et al. (see entire document) teach a method for producing antibodies in vaccinia infected cells that reads on the presently claimed invention (e.g., see Rowlands et al., abstract). For example, Rowlands et al. teach **[a-c]** the use of a population of mammalian host cells (e.g., see page 4, paragraph 2; see also paragraph bridging pages 7-8) for introducing and expressing a first/second polynucleotide encoding, through operable association with a transcriptional control region a first/second immunoglobulin polypeptide comprising both heavy/light chain constant/variable regions and a signal peptide for secretion using a vaccinia virus vector

(e.g., see claim 9, "A process ... compris[ing] ... transfecting the infected cells with a transfer vector [i.e., introducing a polynucleotide] containing DNA encoding the light and ... heavy chain of the antibody under control of a suitable promoter"; see also page 2, middle paragraph, "An antibody molecule is composed of two light chains and two heavy chains ... Each heavy chain has at one end a variable domain followed by a number of constant domains, and each light chain has a variable domain at one end and a constant domain at the other end"; see especially page 4, second full paragraph, "It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form"; see also page 6, paragraphs 1 and 2). Rowlands et al. do not explicitly state that a "signal" peptide is being used, but the Examiner contends that this feature is inherent in the method disclosed by Rowlands et al. because the fully functional recombinant antibody would not be "secreted" unless it has such a sequence. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the Appellants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). Alternatively, the Examiner contends that the phrase "wherein said second immunoglobulin subunit polypeptide is "capable of" combining with said first

immunoglobulin subunit polypeptide to from an immunoglobulin molecule (e.g., see claim 84, step (b)(iii)) has not been afforded any patentable weight. It has been held that the recitation that an element is "capable of" performing a function is not a positive limitation but only requires the ability to so perform. It does not constitute a limitation in any patentable sense. *In re Hutchison*, 69 USPQ 138, 141.

In addition, Rowlands et al. disclose **[d]** contacting said immunoglobulin molecules with an antigen and detecting specific antigen-antibody complexes (e.g., see pages 18-19 and Table I wherein the Campath 1H antigen was "contacted" with said immunoglobulin molecules and "detection" was carried out using both T-cell and antigen binding assays). Finally, Rowlands et al. disclose **[e]** recovering the vaccinia virus vectors containing polynucleotides of said first library which encode immunoglobulin subunits polypeptides which, as part of an immunoglobulin molecule are specific for said antigen (e.g., see page 5, paragraph 1, step 4, wherein the virus is "harvested" several times [i.e., recovered and/or isolated]).

For ***claim 103***, Rowlands et al. disclose a T7 phage promoter active in cells in which T7 RNA polymerase is expressed (e.g., see page 8, paragraph 2, "Expression levels of the two chains of the antibody can be enhanced by use of T7 polymerase to amplify the gene under the control of the T7 promoter").

For ***claims 121-122***, Rowlands et al. disclose ELISA (e.g., see page 18, line 7).

The prior art teachings of Rowlands et al. differ from the claimed invention as follows:

For ***claim 84***, Rowlands et al. are deficient in that they do not specifically teach

the use of a "library" of first/second polynucleotides.

For ***claims 89-91***, Rowlands et al. do not disclose repetitive steps for "biopanning" a library.

For ***claims 92-95***, Rowlands et al. do not provide "isolating" steps.

For ***claim 99***, Rowlands et al. do not disclose an MOI of 1.

For ***claim 107, 110, 127-131***, Rowlands et al. do not disclose method steps for "tri-molecular" recombination.

For ***claims 108-109, 111-112***, Rowlands et al. do not disclose v7.5/tk or vEL/tk virus genomes with NotI/ApaI restriction sites.

For ***claims 114-116, 118-120***, Rowlands et al. do not disclose the use of virus "pools."

However, Zauderer et al. and Waterhouse et al. teach the following limitations that are deficient in Rowlands et al.:

For ***claim 84***, Zauderer et al. (see entire documents) teach the use of a "library" of polynucleotides in a vaccinia virus vector using the "tri-molecular recombination" approach for screening purposes (e.g., see Zauderer et al., page 52, lines 13-16, "The high yield of viral recombinants in tri-molecular recombination makes it possible, for the first time, to efficiently construct genomic or cDNA libraries in a vaccinia virus derived vector"; see also page 15, paragraph 1; see also page 22, last two paragraphs; see also Example 6 on pages 42-52; see also Zauderer et al., pages 49 and 50 wherein "multiple" libraries are produced; see also constructs in figure 2). In addition, Waterhouse et al. teach that a "library" can be usefully employed to screen for antibodies with high affinity

to various antigens including the use of heavy/light chains that are "packaged together" i.e., two libraries (see Waterhouse et al., page 2265, column 1; see also paragraph bridging pages 2265-2266, "... creation of extremely large combinatorial repertoires [is possible]... for example by providing a light chain repertoire in A [i.e., library number 1] and a heavy chain repertoire in B [i.e., library number 2]"). The Examiner further notes that Appellants' elected mammalian "HeLa" cells are disclosed also by Zauderer et al. (e.g., see Zauderer et al., page 32, line 2).

For ***claims 89-91***, Zauderer et al. disclose the use of vaccinia virus library vectors that require the use of a helper virus (i.e., are "incapable of producing infectious vaccinia virus") to infect host cells (e.g., see Zauderer et al., paragraph bridging pages 97-98, "Vaccinia virus DNA is not infectious as the virus cannot utilize cellular transcriptional machinery ... Previously ... non-homologous poxvirus fowlpox ... have been utilized as helper virus for packaging"). Zauderer et al. also indicate that the steps for introducing said vectors into host cells, permitting the expression of said vectors, contacting said expressed antibodies with an antigen and recovering said vectors can be repeated as needed to increase the specificity and/or binding affinity (e.g., see page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure").

For ***claims 92-95***, Zauderer et al. disclose "isolating" the polynucleotides contained in the vaccinia virus vectors (e.g., see Zauderer et al., page 52, lines 20-23; see also page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment

obtained by this procedure [i.e., involves combining isolated fractions]").

For ***claim 99***, Zauderer et al. disclose, for example an MOI = 1 (e.g., see page 86, line 2).

For ***claims 107, 110, 127-131***, Zauderer et al. disclose "tri-molecular" recombination, which includes, for example, cleavage of v7.5/tk or vEL/tk virus genomes with NotI/ApaI restriction enzymes and "one" transfer plasmid containing TKL/TKR and a library of human immunoglobulin genes containing both heavy and light genes to form vaccinia virus vectors via homologous recombination and method steps for screening and purifying said vectors repeated as many times as are needed to produce the desired products (e.g., see pages 48-52, sections 5.2-5.3; see also page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure [i.e., involves combining isolated fractions]"; see also claim 9, "A process ... compris[ing] ... transfecting the infected cells with a transfer vector [i.e., introducing a polynucleotide] containing DNA encoding the light and ... heavy chain of the antibody under control of a suitable promoter").

For ***claims 108, 111***, Zauderer et al. disclose both v7.5/tk and vEL/tk (e.g., see figure 1).

For ***claims 109, 112***, Zauderer et al. disclose both NotI and ApaI (e.g., see figure 10).

For ***claims 114-116, 118-120***, Zauderer et al. disclose the use of "virus pools" (e.g., see page 51, last paragraph, especially line 27; see also page 58, Table V wherein

multiple cycles are disclosed; see also page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure [i.e., involves combining isolated fractions]").

It would have been *prima facie* obvious to of ordinary skill in the art at the time the invention was made to make a library of vaccinia virus vectors as taught by Zauderer et al. to express fully functional antibodies as taught by Rowlands et al. for the purpose of screening and/or affinity maturation as taught by Waterhouse et al. because Zauderer et al. explicitly state that their libraries can be efficiently produced using the tri-molecular recombination approach with the vaccinia virus vectors (like the vaccinia virus vectors disclosed by Rowlands et al.) and Waterhouse et al. teach that such a library would be useful in screening and affinity maturation. Thus, one of ordinary skill in the art would have been motivated to make the libraries as taught by Zauderer et al. using the heavy/light chain antibodies as disclosed by Rowlands et al. because Zauderer et al. explicitly state that the their "tri-molecular" approach represents an easy and efficient means for generating a library in vaccinia virus vectors in mammalian cells, which is a preferred embodiment for Rowlands et al. (e.g., see Zauderer et al., page 22, lines 14-17, "Major advantages of these infectious [vaccinia] viral vectors are ... the ease and efficiency with which recombinants can be introduced mammalian cells"; see also Rowlands et al., page 4, paragraph 2, "One advantage of this system is the authenticity of gene products, particularly those requiring processing and post-translational modification such as glycosylation. This may be particularly important for genes of mammalian

origin"; see also page 52 of Zauderer, middle paragraph, "The above-described tri-molecular recombination strategy yields close to 100% viral recombinants. This is a highly significant improvement over current methods for generating viral recombinants by transfection of a plasmid transfer vector into vaccinia virus infected cells. This latter procedure yields viral recombinants at a frequency of the order of only 0.1%."). In addition, Waterhouse et al. teach that "associated" light and heavy chains are a "preferred" embodiment for screening and/or affinity maturation because they can be "simultaneously co-selected" (e.g., see Waterhouse et al., page 2265, paragraph 2; see also page 2265, column 1; see also paragraph bridging pages 2265-2266 wherein the usefulness of combinatorial antibody libraries is disclosed), which would encompass the "associated" heavy/light chains described by Rowlands et al. In addition, Waterhouse et al. also teach that larger "primary" repertoires of antibodies "should allow higher affinity fragments to be isolated" (e.g., see Waterhouse et al., page 2265, column 1, paragraph 1; see also page 2266, column 1, paragraph 1), which can be easily produced by varying providing "a light chain repertoire in A and a heavy chain repertoire in B" (i.e., producing two libraries simultaneously). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because Zauderer et al. teach several successful examples of library formation using the same vaccinia virus vectors that are disclosed by Rowlands et al. and Waterhouse et al. teach several successful examples of associated light/heavy chains that can be used for screening and/or antibody maturation, which would encompass the heavy/light chain antibodies disclosed by Rowlands et al. In addition, Rowlands et al. state that the use of vaccinia virus as vectors is well known and

has wide applications and explicitly state that it can be used for antibody production (e.g., see Rowland et al., page 4, first full paragraph, "The use of vaccinia virus as a vector for expression of foreign genes has been employed for almost a decade ..."; see also paragraph bridging pages 9 and 10, "the versatility of the method to the present invention means that it will usually be possible to select a type of cell that carries out the processing necessary to produce a fully functional antibody").

Double Patenting

Claims 84, 88-97, 99, 103, 107-122 and 127-131 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-84 of U.S. Patent Application Pub. No. 2003/0104402 A1 (referred to herein as '402) (i.e., Application No. 10/052,942) in view of Rowlands et al. (WO 93/01296) (Date of Patent is **January 21, 1993**).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examiner application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1986).

Here, claims 1-84 of U.S. Patent No. '402 recite a method for selecting polynucleotides which encode immunoglobulin molecules which is essentially the same as that disclosed by claims 84, 88-97, 99, 103, 107-122 and 127-131 in the present

application (e.g., both methods disclose eukaryotic host cells, a first and second library of polynucleotides encoding immunglobulin light/heavy chain constant/variable regions, permitting expression of said immunoglobulin molecules, contacting the molecules with an antigen, recovering the polynucleotides that encode for immunoglobulins that bind to said antigens, etc). The method of claims '402 differ from the present application in that they claim "intracellular" as opposed to "extracellular" expression.

However, Rowlands et al. teach the use of a population of mammalian host cells (e.g., see page 4, paragraph 2; see also paragraph bridging pages 7-8) for introducing and expressing a first/second polynucleotide encoding, through operable association with a transcriptional control region a first/second immunoglobulin polypeptide comprising both heavy/light chain constant/variable regions and a signal peptide for secretion using a vaccinia virus vector i.e., "extracellular" expression (e.g., see claim 9, "A process ... compris[ing] ... transfecting the infected cells with a transfer vector [i.e., introducing a polynucleotide] containing DNA encoding the light and ... heavy chain of the antibody under control of a suitable promoter"; see also page 2, middle paragraph, "An antibody molecule is composed of two light chains and two heavy chains ... Each heavy chain has at one end a variable domain followed by a number of constant domains, and each light chain has a variable domain at one end and a constant domain at the other end"; see especially page 4, second full paragraph, "It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be

recovered in functional form"). Rowlands et al. do not explicitly state that a "signal" peptide is being used, but the Examiner contends that this feature is inherent in the method disclosed by Rowlands et al. because the fully functional recombinant antibody would not be "secreted" unless it has such a sequence i.e., Rowlands et al. teach "extracellular" expression. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the Appellants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Thus, it would have been obvious to modify the method of claims 1-84 of U.S. Patent Pub. No. '402 such that "extracellular" expression was performed instead of "intracellular" expression because Rowlands et al. teach that "extracellular" expression may be obtained within Appellants' preferred vaccinia virus vector. One having ordinary skill in the art would have been motivated to make such a modification because Rowlands et al. teach that their "extracellular" expression is particularly well suited for genes of mammalian origin (e.g., see page 4, first full paragraph), which is a preferred embodiment of the '402 patent application (e.g., see claim 26 of '402). In addition, Rowlands et al. teach that their "extracellular" expression techniques are advantageous "particularly in terms of versatility and speed [because] ... [the] virus will infect a wide range of cells [and] ... [thus] Cell lines suitable for production of a recombinant antibody

can thus be derived conveniently and quickly. (e.g., see Rowlands et al., paragraph bridging pages 9-10). Furthermore, Rowland et al. teach that "extracellular" screening can be useful in tumor diagnosis and/or analysis (e.g., see page 9, lines 1-4; see also examples wherein Campath antigen is used). Finally, a person of skill in the art would have reasonably expected to be successful because Rowlands et al. explicitly state that the vaccinia virus vectors used in '402 can be manipulated to secrete antibodies (e.g., see especially page 4, second full paragraph, "It has now been found that vaccinia virus vectors [i.e., the animal virus disclosed in '402] can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is ***secreted into the medium*** and can thus be recovered in functional form").

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 84, 88-97, 99, 103, 107-122 and 127-131 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 46-128 of U.S. Patent Application 10/465,808 (referred to herein as '808) (US 2005/196755) in view of Rowlands et al. (WO 93/01296) (Date of Patent is **January 21, 1993**) in view of Rowlands et al. (WO 93/01296) (Date of Patent is **January 21, 1993**) and Zauderer et al. (WO 00/28016) (Date of Patent is **May 18, 2000**). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examiner application claim is not patentably distinct from the reference claim(s) because the examined

claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1986).

For ***claim 84, 88, 96-97, 113, 117***, the '808 application discloses a method for selecting polynucleotides which encode an antigen-specific human immunoglobulin molecule (e.g., see '808, claim 46). The '808 application also disclose **(a)** introducing into a population of mammalian host cells capable of expressing said immunoglobulin molecule and permissive for vaccinia virus infectivity (e.g., see claim 46, step (a); see also claim 80 disclosing the use of mammalian host cells which would inherently be permissive for vaccinia virus infectivity). The '808 application also discloses a first library of polynucleotides encoding through operable association with a transcriptional control region, a plurality of first immunoglobulin subunit polypeptides (e.g., see '808 application, claim 46, step (a); see also claims 59 and 68 disclosing constant heavy chain region; see also claims 128). In addition, the '808 application discloses each first immunoglobulin subunit polypeptide comprising **(i)** a first immunoglobulin constant region selected from the group consisting of a heavy chain constant region and a light chain constant region (e.g., see '808, claim 46 claim 128, step (a)(i)). The '808 application also discloses **(ii)** an immunoglobulin variable region selected from the group consisting of a heavy chain variable region and a light chain variable region wherein said variable region corresponds to said first constant region (e.g., see '808, claim 46(a)(ii);). The '808 application also discloses **(iii)** a signal peptide capable of directing cell surface expression or secretion of said first immunoglobulin subunit polypeptide (e.g., see '808

claim 46(a)(iii)). The '808 application also discloses **(b)** introducing into said host cells a second library of polynucleotides encoding through operable association with a transcriptional control region a plurality of second immunoglobulin subunit polypeptides each comprising (e.g., see '808, claim 46(b); see also claim 80). In addition, the '808 application discloses **(i)** a second immunoglobulin constant region selected from the group consisting of a heavy chain constant region or a light chain constant region wherein said second immunoglobulin constant region is not the same as said first immunoglobulin constant region (e.g., see '808, claim 46(b)(i)). The '808 application also discloses **(ii)** an immunoglobulin variable region selected from the group consisting of heavy chain variable region ad a light chain variable region, wherein said variable region corresponds to said second constant region (e.g., see '808, claim 46(b)(ii). The'808 application also discloses **(iii)** a signal peptide capable of directing cell surface expression or secretion of said second immunoglobulin subunit (e.g., see '808, claim 46(b)(iii)). The '808 also discloses said second immunoglobulin subunit polypeptide that is capable of combining with said first immunoglobulin polypeptide to form an immunoglobulin molecule (e.g., see claim 46(b)(iii)). Finally, the '808 application teaches (c)-(e) permitting expression of immunoglobulin molecules, contacting said immunoglobulin molecules with an antigen, detecting specific antigen-antibody complexes and recovering polynucleotides of said first library which encode immunoglobulin subunit polypeptides (e.g., see claim 46(b)(iii)).

For ***claims 89-91***, the '808 application disclose repetitive steps for "biopanning" a library (e.g., see '808, 48, 52, 115 and 123).

For ***claims 92-95***, the '808 application disclose "isolating" steps (e.g., see '808, see claims 49 and 53).

For ***claim 99***, the '808 application also discloses an MOI of 1 to 10 (e.g., see '808, claim 76).

For ***claim 103***, the '808 application also disclose T7 promoter (e.g., see '808 application, claim 96).

For ***claim 107, 110, 127-131***, the '808 application disclose method steps for "tri-molecular" recombination (e.g., see '808, claim 98, 99 and 128).

For ***claims 114-116, 118-120***, the '808 application disclose the use of virus "pools." (e.g., see '808, claims 113, 114, 119, 121)

The '808 differs from the claimed invention as follows:

For ***claim 84***, '808 fails to disclose the use of a vaccinia virus. The 808 application only discloses the use of a eukaryotic virus vector such as a poxvirus vector vector (e.g., see '808, claims 72, 73, 78, 79 and 85-88).

For ***claims 108-109, 111-112***, the '808 application fails to disclose v7.5/tk or vEL/tk virus genomes with NotI/ApaI restriction sites.

For ***claims 121-122***, the '808 application fail to disclose ELISA (e.g., see page 18, line 7).

However, Rowlands et al. and Zauderer et al. teach the following limitations that are deficient in abc et al.:

For ***claim 84***, Rowlands et al. and Zauderer et al. (see entire documents) teach the use of vaccinia virus. For example, Rowlands et al. teach a method for producing

antibodies in vaccinia infected cells that reads on the presently claimed invention (e.g., see Rowlands et al., abstract). Furthermore, Rowlands et al. teach the use of a population of mammalian host cells (e.g., see page 4, paragraph 2; see also paragraph bridging pages 7-8) for introducing and expressing a first/second polynucleotide encoding, through operable association with a transcriptional control region a first/second immunoglobulin polypeptide comprising both heavy/light chain constant/variable regions and a signal peptide for secretion using a vaccinia virus vector (e.g., see claim 9, "A process ... compris[ing] ... transfecting the infected cells with a transfer vector [i.e., introducing a polynucleotide] containing DNA encoding the light and ... heavy chain of the antibody under control of a suitable promoter"; see also page 2, middle paragraph, "An antibody molecule is composed of two light chains and two heavy chains ... Each heavy chain has at one end a variable domain followed by a number of constant domains, and each light chain has a variable domain at one end and a constant domain at the other end"; see especially page 4, second full paragraph, "It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form"; see also page 6, paragraphs 1 and 2). Rowlands et al. do not explicitly state that a "signal" peptide is being used, but the Examiner contends that this feature is inherent in the method disclosed by Rowlands et al. because the fully functional recombinant antibody would not be "secreted" unless it has such a sequence. "When the PTO shows a sound basis for believing that the products of the applicant and

the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the Appellants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). In addition, Rowlands et al. disclose contacting said immunoglobulin molecules with an antigen and detecting specific antigen-antibody complexes (e.g., see pages 18-19 and Table I wherein the Campath 1H antigen was "contacted" with said immunoglobulin molecules and "detection" was carried out using both T-cell and antigen binding assays). Finally, Rowlands et al. disclose recovering the vaccinia virus vectors containing polynucleotides of said first library which encode immunoglobulin subunits polypeptides which, as part of an immunoglobulin molecule are specific for said antigen (e.g., see page 5, paragraph 1, step 4, wherein the virus is "harvested" several times [i.e., recovered and/or isolated]).

In addition, Zauderer et al. (see entire documents) teach the use of a "library" of polynucleotides in a vaccinia virus vector using the "tri-molecular recombination" approach for screening purposes (e.g., see Zauderer et al., page 52, lines 13-16, "The high yield of viral recombinants in tri-molecular recombination makes it possible, for the first time, to efficiently construct genomic or cDNA libraries in a vaccinia virus derived vector"; see also page 15, paragraph 1; see also page 22, last two paragraphs; see also Example 6 on pages 42-52). In addition, Waterhouse et al. teach that a "library" can be usefully employed to screen for antibodies with high affinity to various antigens including the use of heavy/light chains that are "packaged together" i.e., two libraries (see

Waterhouse et al., page 2265, column 1; see also paragraph bridging pages 2265-2266, "... creation of extremely large combinatorial repertoires [is possible]... for example by providing a light chain repertoire in A [i.e., library number 1] and a heavy chain repertoire in B [i.e., library number 2]"). The Examiner further notes that Appellants' elected mammalian "HeLa" cells are disclosed also by Zauderer et al. (e.g., see Zauderer et al., page 32, line 2).

For ***claims 89-91***, Zauderer et al. also disclose the use of vaccinia virus library vectors that require the use of a helper virus (i.e., are "incapable of producing infectious vaccinia virus") to infect host cells (e.g., see Zauderer et al., paragraph bridging pages 97-98, "Vaccinia virus DNA is not infectious as the virus cannot utilize cellular transcriptional machinery ... Previously ... non-homologous poxvirus fowlpox ... have been utilized as helper virus for packaging"). Zauderer et al. also indicate that the steps for introducing said vectors into host cells, permitting the expression of said vectors, contacting said expressed antibodies with an antigen and recovering said vectors can be repeated as needed to increase the specificity and/or binding affinity (e.g., see page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure").

For ***claims 92-95***, Zauderer et al. also disclose "isolating" the polynucleotides contained in the vaccinia virus vectors (e.g., see Zauderer et al., page 52, lines 20-23; see also page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment

obtained by this procedure [i.e., involves combining isolated fractions]").

For ***claim 99***, Zauderer et al. also disclose, for example an MOI = 1 (e.g., see page 86, line 2).

For ***claim 103***, Rowlands et al. also disclose a T7 phage promoter active in cells in which T7 RNA polymerase is expressed (e.g., see page 8, paragraph 2, "Expression levels of the two chains of the antibody can be enhanced by use of T7 polymerase to amplify the gene under the control of the T7 promoter").

For ***claims 107, 110, 127-131***, Zauderer et al. also disclose "tri-molecular" recombination, which includes, for example, cleavage of v7.5/tk or vEL/tk virus genomes with NotI/ApaI restriction enzymes and "one" transfer plasmid containing TKL/TKR and a library of human immunoglobulin genes containing both heavy and light genes to form vaccinia virus vectors via homologous recombination and method steps for screening and purifying said vectors repeated as many times as are needed to produce the desired products (e.g., see pages 48-52, sections 5.2-5.3; see also page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure [i.e., involves combining isolated fractions]"; see also claim 9, "A process ... compris[ing] ... transfecting the infected cells with a transfer vector [i.e., introducing a polynucleotide] containing DNA encoding the light and ... heavy chain of the antibody under control of a suitable promoter").

For ***claims 108, 111***, Zauderer et al. disclose both v7.5/tk and vEL/tk (e.g., see figure 1).

For ***claims 109, 112***, Zauderer et al. disclose both NotI and ApaI (e.g., see figure 10).

For ***claims 114-116, 118-120***, Zauderer et al. also disclose the use of "virus pools" (e.g., see page 51, last paragraph, especially line 27; see also page 58, Table V wherein multiple cycles are disclosed; see also page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure [i.e., involves combining isolated fractions]").

For ***claims 121-122***, Rowlands et al. disclose ELISA (e.g., see page 18, line 7).

It would have been *prima facie* obvious to one of ordinary skill in the art to select vaccinia virus as taught by the combined references of Zauderer et al. and Rowlands et al. as the eukaryotic virus vector as taught by the '808 patent application because Zauderer et al. explicitly state that their libraries can be efficiently produced using the tri-molecular recombination approach with the vaccinia virus vectors (like the vaccinia virus vectors disclosed by Rowlands et al.). Thus, one of ordinary skill in the art would have been motivated to make the libraries as taught by Zauderer et al. using the heavy/light chain antibodies as disclosed by Rowlands et al. and the'808 application because Zauderer et al. explicitly state that the their "tri-molecular" approach represents an easy and efficient means for generating a library in vaccinia virus vectors in mammalian cells, which is a preferred embodiment for Rowlands et al. (e.g., see Zauderer et al., page 22, lines 14-17, "Major advantages of these infectious [vaccinia] viral vectors are ... the ease and efficiency with which recombinants can be introduced mammalian cells"; see also

Rowlands et al., page 4, paragraph 2, "One advantage of this system is the authenticity of gene products, particularly those requiring processing and post-translational modification such as glycosylation. This may be particularly important for genes of mammalian origin"). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because Zauderer et al. teach several successful examples of library formation using the same vaccinia virus vectors that are disclosed by Rowlands et al. and the '808 application. Furthermore, a person of ordinary skill in the art would reasonably have expected to be successful because Rowlands et al. state that the use of vaccinia virus as vectors is well known and has wide applications and explicitly state that it can be used for antibody production (e.g., see Rowland et al., page 4, first full paragraph, "The use of vaccinia virus as a vector for expression of foreign genes has been employed for almost a decade ..."; see also paragraph bridging pages 9 and 10, "the versatility of the method to the present invention means that it will usually be possible to select a type of cell that carries out the processing necessary to produce a fully functional antibody") and also provide successful examples of antibody expression using vaccinia.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

(10) Response to arguments

Claim Rejections - 35 USC § 103

Argument 1

Appellants first argue that there was no reasonable expectation of success stating, "Even assuming, arguendo, that one of ordinary skill in the art would know in view of Rowlands how to express a single antibody, and would know in view of Zauderer how to make and screen a single vaccinia virus expression library, it does not follow that the skilled artisan could, with a reasonable expectation of success, arrive at a method of selecting polynucleotides encoding antigen-specific immunoglobulins by introducing two libraries of vaccinia virus vectors into mammalian host cells" (e.g., see 7/6/07 Appeal Brief, paragraph bridging pages 12 and 13; see also pages 6-12 for general legal background and brief summary of prior art references).

Response 1

The Examiner respectfully disagrees. A person of ordinary skill would not change the amino acids known to be responsible for the heavy and light chain association. Antibodies are well-characterized molecules. Their structures are well known and taught in nearly all-rudimentary biochemistry textbooks. Thus, a person of ordinary skill would not expect the introduction of a library into the variable regions of the heavy/light chain to interfere with these associations. It is skill, not stupidity, which is presumed in the art. *In re Sovish*, 769 F.2d 738, 743, 226 USPQ 771, 774 (Fed. Cir. 1985).

Furthermore, the Examiner notes that obviousness does not require absolute predictability of success; rather, all that is required for obviousness under § 103 is a "reasonable expectation of

success." *In re O'Farrell*, 853 F.2d at 903-904 [7 USPQ2d at 1681]. Here, Rowlands et al. teach a method for producing antibodies in vaccinia infected "mammalian" cells (e.g., see Rowlands et al. page 4, paragraph 2; see also paragraph bridging pages 7-8). Thus, the conclusion that a person of skill in the art would know how to express an antibody in a "mammalian" cell is reasonable. Zauderer et al. teach how to make and/or use a library of proteins using a vaccinia virus vector like the vaccinia virus vector disclosed by Rowlands (e.g., see Zauderer et al., page 52, lines 13-16, "The high yield of viral recombinants in tri-molecular recombination makes it possible, for the first time, to efficiently construct genomic or cDNA libraries in a vaccinia virus derived vector"; see also page 15, paragraph 1; see also page 22, last two paragraphs; see also Example 6 on pages 42-52). Thus, the conclusion that a person of skill in the art would know how to make and/or use a library of proteins, including antibodies, with a vaccinia virus is reasonable. That is, the Zauderer et al. reference never states or indicates in any way that the use of tri-molecular recombination should somehow limited to expressing only one particular class of proteins (i.e., everything but Appellants' claimed antibodies). Finally, Waterhouse et al. teach the co-selection of a library of heavy and light chains (i.e., the use of two libraries) and thus a conclusion that these two libraries would be "capable" of combining together is reasonable since co-selection could not be performed without it. In addition, it can also be "inferred" from Waterhouse et al. that the advantages of co-selection would be just as applicable to mammalian systems as to prokaryotic systems disclosed therein because antibody selection depends on the structure of the antibody, not the source from which it was obtained (i.e., an antibody produced in a eukaryotic host would have the exact same binding affinity as an identical antibody produced in a prokaryotic host for a given antigen). This teaching is further

"augmented" by Rowlands et al. who present a facile method for expressing antibodies (both heavy and light chains) in eukaryotic systems and Zauderer et al. who present a facile method for producing "libraries of proteins" in these same hosts

Finally, it should be noted that Appellants' arguments are not commensurate in scope with the claims. Independent claim 84, for example, only requires that the first and second immunoglobulin subunits be "capable of" combining together. An actual combination of the two is not required by the claims (emphasis added). Clearly, a person of ordinary skill in the art would expect a heavy and a light chain to be "capable" of association whether such association was actually found in practice or not.

Argument 2

Appellants argue, "Dr. Storkus ... did not think there was a reasonable expectation of success and he provided specific reasons why he considered phage display methods, such as those ... disclosed in Waterhouse, to be of limited instructive value for a eukaryotic immunoglobulin screening method ... [because of] the complexity of getting randomly expressed immunoglobulin heavy and light chains from two different libraries to associate [in eukaryotic systems] ... Furthermore, Dr. Storkus indicated that a eukaryotic cell system was though to be impractical for screening a sufficient number of eukaryotic cells to find an antibody that had specificity for a specific antigen of interest" (e.g., see 7/6/07 Appeal Brief, paragraph bridging pages 13 and 14).

Response 2

Again, Appellants arguments (and accompanying declaration) are not commensurate in

scope with the claims (e.g., see *In re Grasselli*, 713 F.2d 731, 741, 218 USPQ 769, 777 (Fed. Cir. 1983) (Claims were directed to certain catalysts containing an alkali metal. Evidence presented to rebut an obviousness rejection compared catalysts containing sodium with the prior art. The court held this evidence insufficient to rebut the *prima facie* case because experiments limited to sodium were not commensurate in scope with the claims); see also *In re Tiffin and Erdman*, 171 USPQ 294 (CCPA 1971) and cases cited therein; see also MPEP § 716.02(d). That is, the claims do not require "efficient" introduction of libraries into hosts cells, "efficient" selection, or even any "association" at all. The light and heavy chains merely need to be "capable" of associating. Independent claim 84, for example, does not set any requirements on the "efficiency" of selection or the resultant quality of the antibody libraries produced. For example, Dr. Storkus never states that he wouldn't expect "any" matching to occur or that the unassociated heavy and light chains would be useful in screening by themselves. As noted previously, Appellants have already admitted that their claimed scope encompasses the use of "low efficiency" methods that generate "poor" antibodies (e.g., see 12/7/04 Response, page 22, "While the specification does indicate that direct ligation results in a relatively low recombination efficiency and titer ... it does not say that methods such as direct ligation or modified homologous recombination [which are included within the scope of Appellants' invention] cannot be used to generate vaccinia virus expression libraries"; see also page 25, first full paragraph, "... direct ligation and modified homologous recombination may be less efficient than tri-molecular recombination ... [however] the specification does not say that they cannot be used") (emphasis added).

Furthermore, the declaration is not consistent with the Zauderer et al. reference, which explicitly states that libraries of proteins can be produced and screened in mammalian cells (e.g.,

see Zauderer et al., claim 14, "wherein the expression library is constructed in a viral vector infectious for mammalian cell"; see also page 52, lines 13-16, "The high yield of viral recombinants in tri-molecular recombination makes it possible, for the first time, to efficiently construct genomic or cDNA libraries in a vaccinia virus derived vector"; see also page 15, paragraph 1; see also page 22, last two paragraphs; see also Example 6 on pages 42-52). Although Zauderer et al. do not explicitly state that "antibodies" can be screened in this fashion, the Zauderer et al. reference never states or indicates in any way that the use of tri-molecular recombination should somehow limited to expressing only one particular class of proteins (i.e., everything but Appellants' claimed antibodies). In addition, it can also be "inferred" from the Waterhouse et al. reference that the advantages of co-selection would be just as applicable to mammalian systems as to prokaryotic systems disclosed therein because antibody selection depends on the structure of the antibody, not the source from which it was obtained (i.e., an antibody produced in a eukaryotic host would have the exact same binding affinity as an identical antibody produced in a prokaryotic host for a given antigen). This teaching is further "augmented" by Rowlands et al. who present a facile method for expressing antibodies (both heavy and light chains).

In addition, the Storkus Declaration is ambiguous. For example, Dr. Storkus states, "At the time the idea for the present invention was presented to me, I did not think that antigen-specific antibodies could be efficiently selected from random libraries of immunoglobulin heavy and light chains expressed in eukaryotic cells in vitro because I thought specific antibodies of interest would occur at relatively low frequency and it would not be practical to screen the number of eukaryotic cells necessary in order to find an antibody that had specificity for a

specific antigen of interest" (e.g., see Storkus Declaration, page 3, paragraph 7). However, Dr. Storkus never states at "what time" was the idea presented to him. Perhaps it was presented to him 20 years ago (i.e., phage display had been around since at least the mid 1980s as evidenced by the work of Smith) when tri-molecular recombination had not yet been invented (i.e., before the Zauderer et al. reference). We don't know what Dr. Storkus would have stated at "the filing date of the application" as required. Thus, these statements provide no evidentiary support for Appellants.

Furthermore, this assertion of "relatively low frequency" in contradicted by the Zauderer et al., reference, the Waterhouse reference and Appellants' own specification. For example, Zauderer et al. state that they can "efficiently" produce libraries and even tout 100% conversion using the tri-molecular approach (e.g., see Zauderer et al., page Detailed Description of the Invention, especially paragraph bridging pages 14 and 15, "In one embodiment of the invention ... [i]mproved and modified vaccinia virus vectors for efficient construction of such DNA libraries using a "trimolecular recombination" approach are described to improve screening efficiency"; see also page 22, last full paragraph; see especially, page 52, middle paragraph, "The above-described tri-molecular recombination strategy yields close to 100% viral recombinants. This is a highly significant improvement over current methods for generating viral recombinants by transfection of a plasmid transfer vector into vaccinia virus infected cells. This latter procedure yields viral recombinants at a frequency of the order of only 0.1%."). Thus, Zauderer et al. explicitly state that they can "increase" their efficiency by exactly "four orders of magnitude" (i.e., 0.1% → 100%) as noted by Appellants above (emphasis added).

In addition, the Storkus declaration never states that adequate diversity could not be

generated using "more than one" library. The declaration, instead, focuses on single chain Fv antibodies, which does not equate to the use of "two" libraries as set forth, for example, by Waterhouse et al. (e.g., see Waterhouse et al., paragraph bridging pages 2265 and 2266, "The process [i.e., the use of "two" libraries] appears to be highly efficient, and should allow the creation of extremely large combinatorial repertoires, for example, by providing a light chain repertoire in A and a heavy chain repertoire in B. It should also facilitate the affinity maturation of antibodies selected from the large libraries by chain shuffling"; see also Appellants' admission in Example 3, "Previous work [i.e., the prior art] employing phage display methods has suggested that for many antigens a library that includes 10^9 immunoglobulin heavy and light chain combinations is of a sufficient size to select a relatively high affinity specific antibody. In principle, it is possible to construct a library with 10^9 recombinants each of which expresses a unique heavy chain and a unique light chain or a single chain construct with a combining site comprising variable regions of heavy and light chains. The most preferred method, however, is to generate this number of antibody combinations by constructing two libraries of 10^5 immunoglobulin heavy chains and 10^4 immunoglobulin light chains that can be co-expressed in all 10^9 possible combinations"). Thus, even Appellants admit that the prior art suggested the creation of larger libraries using "two" libraries of heavy (e.g., 10^5 members) and light (e.g., 10^4 members), which is position that is entirely consistent with the teachings of Waterhouse.

Finally, the Examiner notes that although Dr. Storkus states that he thought "separate libraries would be poorly matched" in mammalian systems because, "[t]he conditions of assembly in the eukaryotic cytoplasm are far different from those that apply in the periplasmic space and it could not be known what effect this would have on antibody assembly" (e.g., see

Storkus Declaration, pages 3 and 4, paragraph 7), Dr. Storkus never explains what the "far different" conditions are upon which the conclusion is based. Thus, there is no factual basis for this "poorly matched" assertion. Furthermore, Appellants are implicitly arguing against the 35 U.S.C. § 103 statute itself, which is impermissible. An obviousness rejection will, as practical mater, necessarily assert the use of a secondary reference (or source) to teach the "new" conditions (i.e., limitations) that are deficient in the primary reference(s) (i.e., "two" libraries in a mammalian cell host in this case). Appellants cannot elevate the standard of non-obviousness under 35 U.S.C. § 103 to one of anticipation under 35 U.S.C. § 102. If "two" libraries in a mammalian host were found in one reference as suggested by Appellants that reference would "anticipate" the claimed invention. This was not the intention of Congress (e.g., see *Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966)).

Argument 3

Appellants argue again that the Examiner has disregarded the Storkus declaration and failed to provide a factual basis for "substituting his opinion for that of an expert" and goes on to note several points made by Dr. Storkus (e.g., see 7/6/07 Appeal Brief, page 14, last paragraph; see also first full paragraph on page 15).

Response 3

The Examiner respectfully disagrees for the reasons stated in Response 2.

Argument 4

Appellants argue, "Dr. Storkus also explicitly stated that Zauderer does not address the concern of assembling heavy and light chains from two separate libraries in eukaryotic cells" (e.g., see 7/6/07 Appeal Brief, page 15, middle paragraph).

Response 4

Again, as noted repeatedly above, Appellants' arguments are not commensurate in scope with the claims. No such "assembly" is required by independent claim 84. The heavy and light subunits merely need to be "capable" of association. Furthermore, Appellants have by making this statement failed to appreciate the teachings of the other references. Clearly, Rowlands et al. teach that a heavy and light chain can be associated together using a vaccinia virus vector (see rejection above). This fact has not been refuted in any way by Dr. Storkus. Furthermore, Dr. Storkus never stated that two libraries could not be introduced into eukaryotic cells. Thus, the declaration by Dr. Storkus does not refute the Examiner's position that two libraries can be introduced into eukaryotic cells that are "capable" of association. In fact, contrary to Appellants' assertions, the declaration by Dr. Storkus admits that two libraries can be introduced into eukaryotic cells with the "capability" of association (e.g., see 4/27/07 Declaration, page 3, paragraph 7 wherein Dr. Storkus stated that he though a "relatively low frequency" would be produced). Here, Appellants' claimed scope (see Response 1 above) encompasses "low frequency" recombination. Furthermore, the Declaration is not consistent with the Zauderer et al. reference, which explicitly states that libraries can be produced for the first time with high efficiency (e.g., see Zauderer et al., page 52, lines 13-16, "The high yield of viral recombinants in tri-molecular recombination makes it possible, for the first time, to efficiently construct

genomic or cDNA libraries in a vaccinia virus derived vector"; see also page 15, paragraph 1; see also page 22, last two paragraphs; see also Example 6 on pages 42-52). That is, the complex nature referred to by Dr. Storkus of the mammalian systems appears to be just as applicable to the libraries produced in the Zauderer et al. reference since they used mammalian systems to produce these libraries. See also Response 2 above.

Argument 5

Appellants argue again that the Examiner has not provided any specific evidence or relevant scientific rational to counter the statements of Dr. Storkus and further argue that the cited passages in Appellants' specification do not support the Examiner's position (e.g., see 7/6/07 Appeal Brief, paragraph bridging pages 15 and 16).

Response 5

The Examiner respectfully disagrees. The declaration by Dr. Storkus has been fully considered but found to be non-persuasive for the reasons set forth in Responses 2 and 4.

Argument 6

Appellants argue, "the Examiner erred factually by contending that the Storkus Declaration is "ambiguous," and that Dr. Storkus did not specify the time at which the idea for the present invention was first presented to him ... It is clear from his Declaration that the idea was presented to Dr. Storkus in his capacity as an SAB member of Vaccinex, Inc., and that he was an SAB member at the time the present application was filed (i.e., from 2001 to 2004)" (e.g., see 7/6/07 Appeal Brief, page 16, last paragraph).

Response 6

The declaration makes no such assertion. The idea could have been presented to Dr. Storkus and the other SAB members before they became SAB members. That is, Dr. Storkus could have been referring to these people by their current SAB status as a convenient means to describe the same group of people before they became SAM members. Furthermore even if, *assuming arguendo*, the declaration by Dr. Storkus could be fairly interpreted to provide a date between 2001 and 2004 as Appellants now contend, the position of Dr. Storkus would still be unclear. For example, if the idea was first presented to Dr. Storkus on September 6, 2004 (i.e., within Appellants' suggested 2001 to 2004 range) then it would call into question his awareness of the relevant prior art since the present Zauderer et al. application was published and made publicly available on September 5, 2002 (as U.S. Pat. Applic. Pub. 2002/0123057 A1) more than 2 years before the information allegedly became available to Dr. Storkus. Thus, it is still unclear when the information was first given to Dr. Storkus and under what circumstances he was making these assertions.

Argument 7

Appellants again argue that there was no reasonable expectation of success since Waterhouse et al. was a method developed for bacterial host cells, not the currently claimed eukaryotic host cells (e.g., see 7/6/07 Appeal Brief, page 17, paragraph 1).

Response 7

The Examiner respectfully disagrees for the reasons set forth above (see especially Response 1).

Argument 8

Appellants argue that the Examiner has not considered the claimed invention as a whole and is using impermissible hindsight to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. More specifically Appellants state, "The Examiner has ... merely substituted the feature of two expression libraries from Waterhouse to 'fill in' the missing element from the Rowlands/Zauderer combination. However, as established in Hybritech, this type of simple substitution of elements is an improper analysis for establishing a prima facie case of obviousness ... it ignores the fact that the Waterhouse immunoglobulin libraries are prokaryotic phage display libraries and the claimed invention requires two eukaryotic expression libraries" (e.g., see 7/6/07 Appeal Brief, pages 17-19, especially page 19, middle paragraph).

Response 8

First, the Examiner notes that Appellants' arguments are unclear. Appellants state that the Examiner has not considered the invention "as a whole" but then fail to provide any explanation for this position. The only gloss provided is on page 19, middle paragraph wherein Appellants further state that the Examiner has ignored the fact that the Waterhouse immunoglobulin libraries are prokaryotic phage display libraries and the claimed invention requires, in contrast, eukaryotic expression libraries. However, this implicit argument that using prokaryotic expression systems could not be extrapolated to eukaryotic cells because the conditions for assembly of immunoglobulins from light and heavy chains are different in the eukaryotic cytoplasm than in the periplasmic space of a bacterial host (e.g., see 2/2/06 Response, page 27, paragraph 2 quoting Storkus Declaration, paragraph 4 wherein a similar argument was made) is not even consistent with Appellants' own specification, which clearly admits that a

person of skill in the art would look, perhaps preferentially, to phage display (i.e., prokaryotic systems). For example, Appellants state, "Previously, three general strategies have been employed to produce immunoglobulin molecules ... is to screen recombinant human antibody fragments displayed on bacteriophage [i.e., a person trying to make antibodies would have routinely looked to this discipline for guidance] ... Examples of phage display methods that can be used to make the antibodies include those disclosed in Brinkman ... Ames, R. S. ... Kettleborough, C. [etc.]" (e.g., see specification, paragraphs 9-11; see also paragraph 12 wherein Appellants' acknowledge that phage display can be used to produce human antibodies; see especially Example 3, paragraph 321 wherein Appellants expressly endorse the use of phage display as a teaching for vaccinia virus vectors i.e., they use the data provided by phage display (109 members will generate a strong binding affinity) to guide their vaccinia virus work). Therefore, Appellants' implicit argument that these two systems do not represent analogous art is without merit. Both papers deal with the production of antibodies and, as a result, represent analogous art (e.g., *see In re Paulsen*, 31 USPQ2d 1671 (Fed. Cir. 1994) (A "clam style" fastening means is not "unique" to the computer industry and, as a result, a person of skill would consult other "mechanical" literature for a solution to this fastening problem).

In addition, the claimed invention has not been boiled down to a "gist" or a "thrust" of the invention as was shown to be improper in cases like *Bausch & Lomb v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 447-49, 230 USPQ 416, 419-20 (Fed. Cir. 1986), cert. denied, 484 U.S. 823 (1987); *Jones v. Hardy*, 727 F.2d 1524, 1530, 220 USPQ 1021, 1026 (Fed. Cir. 1984); and *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1 USPQ2d 1593 (Fed. Cir.), cert. denied, 481 U.S. 1052 (1987). See, for example, MPEP § 2141.02, section II. For example,

the "two" libraries are taught by the "combined" references as outlined in the rejection above. That is, it would be obvious to express "two" libraries of antibodies (heavy in light chains) in the mammalian expression system disclosed by Rowlands et al. for the purposes of screening for higher affinity antibodies as taught by the combined teachings of Zauderer et al. and Waterhouse et al. Thus, the Examiner has not disregarded the claimed features of introducing two vaccinia virus libraries encoding whole immunoglobulin heavy and light chains into mammalian host cells.

Furthermore, Appellants have not alleged or provided any evidence showing a failure to discover a source/cause problem (e.g., see MPEP § 2141.02, sections III and IV). Furthermore, the Examiner has taken into consideration all of the relevant "inherent" features as required, for example, by MPEP § 2141.02, section V (e.g., see above rejection, "Rowlands et al. do not explicitly state that a "signal" peptide is being used, but the Examiner contends that this feature is inherent in the method disclosed by Rowlands et al. because the fully functional recombinant antibody would not be "secreted" unless it has such a sequence."). Finally, the Examiner notes that the previous office action also addressed all of Appellants' "teaching away" arguments as required by MPEP § 2141.02, section VI (e.g., see 4/21/06 Office action, page 25, paragraph 1, especially line 9, "No such "teaching away" exists here"). Thus, the claimed invention has been considered as a whole in accordance with MPEP § 2141.02.

Argument 9

Appellants argue, "As indicated in the declarations of Dr. Storkus (Exhibit 4) and Dr. Maurice Zauderer (submitted herewith as Exhibit 5), the expression of antibody fragments in prokaryotic phage display libraries is fundamentally different from the expression of

immunoglobulins from two eukaryotic libraries and, therefore, the success of the prokaryotic system would not have bee predictive of the success of the eukaryotic system" and cite several passages from the Storkus Declaration that were cited above in support of this position (e.g., see 7/6/07 Appeal Brief paragraph bridging pages 19 and 20).

Response 9

The Examiner respectfully submits that the "reasons for success" argument and the Storkus declaration have been adequately addressed above (e.g., see Responses 1 and 2).

Argument 10

Appellants argue, "Dr. Zauderer indicated that one of ordinary skill in the art would not have considered the Waterhouse improvements to phage display methods ... 'as features that could be expanded for use in eukaryotic systems.' ... it would not have been predictable that separately expressed heavy and light chains from two random vaccinia libraries would find each other in the eukaryotic cytoplasm and pair together with sufficient frequency to form antigen-specific immunoglobulins" (e.g., see 7/6/07 Appeal Brief, page 20).

Response 10

The Examiner respectfully disagrees. The arguments made with regard to the declaration by Dr. Storkus are just as applicable here (see above). Namely, Appellants' arguments are not commensurate in scope with the claims. "Pair[ing] together with sufficient frequency to form antigen-specific immunoglobulins" is not a limitation this is required by the claims. An noted repeatedly above, the heavy and light chains need only be "capable" of pairing. Furthermore, there's no reason to expect "less" pairing that would be formed from the use of two libraries

because the changes made would not affect those parts of the antibody heavy and light chain that are responsible for the pairing. Only the variable regions are affected as exemplified by Waterhouse et al. Furthermore, Rowlands explicitly state that a heavy and light chain will associate. Thus, the assumptions (as set forth in detail above) are entirely reasonable.

In addition, this assertion of "relatively low frequency" in contradicted by the Zauderer et al., reference, the Waterhouse reference and Appellants' own specification. For example, Zauderer et al. state that they can "efficiently" produce libraries and even tout 100% conversion using the tri-molecular approach (e.g., see Zauderer et al., page Detailed Description of the Invention, especially paragraph bridging pages 14 and 15, "In one embodiment of the invention ... [i]mproved and modified vaccinia virus vectors for efficient construction of such DNA libraries using a "trimolecular recombination" approach are described to improve screening efficiency"; see also page 22, last full paragraph; see especially, page 52, middle paragraph, "The above-described tri-molecular recombination strategy yields close to 100% viral recombinants. This is a highly significant improvement over current methods for generating viral recombinants by transfection of a plasmid transfer vector into vaccinia virus infected cells. This latter procedure yields viral recombinants at a frequency of the order of only 0.1%."). Thus, Zauderer et al. explicitly state that they can "increase" their efficiency by exactly "four orders of magnitude" (i.e., 0.1% → 100%) as noted by Appellants above (emphasis added).

Argument 11

Appellants argue, "At the very most, the combination of Rowlands, Zauderer, and Waterhouse might be an invitation to try introducing two expression libraries of immunoglobulin

chains in eukaryotic cells ... [which] is not the standard for establishing a prima facie case of obviousness under 35 U.S.C. § 103" (e.g., see 7/6/07 Appeal Brief, page 21, paragraph 1).

Response 11

In response to Applicant's that the rejection represents only an "obvious to try" rationale, the following paragraph from MPEP 2145 is noted:

> The admonition that obvious to try' is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been obvious to try would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful ... In others, what was obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (citations omitted) (The court held the claimed method would have been obvious over the prior art relied upon because one reference contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful.). Se the cases cited in O'Farrell for examples of decisions where the court discussed an improper "obvious to try" approach. See also In re Eli Lilly & Co., 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) and In re Ball Corp., 925 F.2d 1480, 18 USPQ2d 1491 (Fed. Cir. 1991) (unpublished) for examples of cases where appellants argued that an improper "obvious to try" standard was applied, but the court found that there was proper motivation to modify the references.

Here, the combination of references clearly indicate which parameters are critical and do provide specific guidance as to which of many possible choices is likely to be successful. For example, Rowlands et al. teach that the use of vaccinia virus as vectors is well known and has wide applications and specifically state that it can be used for antibody production (e.g., see Rowland et al., page 4, first full paragraph, "The use of vaccinia virus as a vector for expression of foreign genes has been employed for almost a decade ..."; see also paragraph bridging pages 9 and 10, "the versatility of the method to the present invention means that it will usually be possible to select a type of cell that carries out the processing necessary to produce a fully functional antibody"). Thus, a person of ordinary skill in the art would know which parameters are critical to express an antibody in a eukaryotic cell. Furthermore, Zauderer provides a facile method for

expressing libraries using the same vaccinia virus that is presented in Rowlands et al. and, a result, one of ordinary skill would also know which parameters are critical to form a library in eukaryotic cells. Thus, a person of skill in the art would know how to form a library of antibodies. The proposition that a person of skill in the art would somehow "forget" how to do this when faced when with the task of producing a "second" library has no basis in fact. Furthermore, the courts have repeatedly held that the mere "duplication" or "scale up" (i.e., one library to two) is *prima facie* obvious unless some unexpected results are obtained (e.g., *see In re Rinehart*, 531 F.2d. 1048, 189 U.S.P.Q. 143 (C.C.P.A. 1976); see also see *In re Harza*, (274 F.2d 669, 124 USPQ 378 (CCPA 1960)), which is not the case here.

In addition, the Supreme Court has reversed this misuse of "rigid preventive rules" in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. __, 2007 WL 1237837, at *7 (2007) ("the Court of Appeals ... conclude[d], in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try" ... Rigid preventative rules that deny fact finders recourse to common sense, however, are neither necessary under our [Supreme Court] case law nor consistent with it").

Argument 12

Appellants argue that their previous arguments are consistent with the recent KSR and Takeda Chemical Industries decisions and further confirm that their previous statements with regard to the Storkus declaration and the "reasonable expectation of success" argument still remain in effect (e.g., see 7/6/07 Appeal Brief, pages 21 and 22).

Response 12

The Examiner respectfully submits that the "reasonable expectation of success" argument and the declaration by Dr. Storkus were adequately addressed above (e.g., see especially Responses 1 and 2).

Argument 13

Appellants again reiterate their "claimed invention as a whole" argument noting that KSR is not inconsistent with the proposition that the Examiner must consider the claimed invention as a whole (e.g., see 7/6/07 Response, page 23, paragraph 1).

Response 13

The Examiner respectfully submits that the "claimed invention as a whole" argument ahs been adequately addressed above (e.g., see Response 8).

Argument 14

Appellants argue, "as demonstrated in Takeda, there is no general rule that modifications of chemical structure are obvious per se ... the present invention was not derived by merely 'optimizing' or 'tweaking' certain known parameters of a prior art method ... unlike Pfizer, the art did not provide any guidance that would have led one of ordinary skill to the methods of the present invention with a reasonable expectation of success" (e.g., see 7/6/07 Appeal Brief, page 24, last two paragraphs).

Response 14

The Examiner again respectfully submits that the "reasonable expectation of success" argument and the declaration by Dr. Storkus have been adequately addressed above (e.g., see Responses 1 and 2 above).

Argument 15

Appellants additionally argue in the conclusion section that there is no motivation to combine the references, that all limitations have not been taught and that impermissible hindsight has been used (e.g., see 7/6/07 Appeal Brief, page 26, middle paragraph).

Answer 15

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one of ordinary skill in the art would have been motivated to make the libraries as taught by Zauderer et al. using the heavy/light chain antibodies as disclosed by Rowlands et al. because Zauderer et al. explicitly state that the their "tri-molecular" approach represents an easy and efficient means for generating a library in vaccinia virus vectors in mammalian cells, which is a preferred embodiment for Rowlands et al. (e.g., see Zauderer et al., page 22, lines 14-17, "Major advantages of these infectious [vaccinia] viral vectors are ... the ease and efficiency with which

recombinants can be introduced mammalian cells"). In addition, Waterhouse et al. teach that "associated" light and heavy chains are a "preferred" embodiment for screening and/or affinity maturation because they can be "simultaneously co-selected" (e.g., see Waterhouse et al., page 2265, paragraph 2; see also page 2265, column 1; see also paragraph bridging pages 2265-2266 wherein the usefulness of combinatorial antibody libraries is disclosed), which would encompass the "associated" heavy/light chains described by Rowlands et al. In addition, Waterhouse et al. also teach that larger "primary" repertoires of antibodies "should allow higher affinity fragments to be isolated" (e.g., see Waterhouse et al., page 2265, column 1, paragraph 1; see also page 2266, column 1, paragraph 1), which can be easily produced by varying providing "a light chain repertoire in A and a heavy chain repertoire in B" (i.e., producing two libraries simultaneously).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must again be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In addition, "The presence or absence of a motivation to combine references in an obviousness determination is a pure question of fact." *In re Gartside*, 203 F3d 1305, 1316, 53 USPQ2d 1769, 1776 (Fed. Cir. 2000) (citing *In re Dembiczak*, 175 F.3d 994, 1000, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999). "'[T]he question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination.'" In re

Beattie, 974 F.2d 1309, 1311-12, 24 USPQ2d 1040, 1042 (Fed. Cir. 1992) (quoting Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1462, 221 USPQ 481, 488 (Fed. Cir. 1984)). "[E]vidence of a suggestion, teaching, or motivation to combine may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. . . ." Dembiczak, 175 F.3d at 999, 50 USPQ2d at 1617 (citing Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1630 (Fed. Cir. 1996); Para-Ordnance Mfg. v. SGS Imports Int'l, Inc., 73 F.3d 1085, 1088, 37 USPQ2d 1237, 1240 (Fed. Cir. 1995)). Here, the references themselves, not Appellants' specification, provides ample motivation for their combination as set forth in the rejection above (e.g., see rejection above wherein "motivation" is explicitly correlated to each individual reference by page and line number).

Finally, Appellants have failed to assert that any of the reasoning set forth in the obviousness rejection above took into account knowledge gleaned only from Appellants' disclosure. To the contrary, Appellants merely stated that you couldn't combine the three references, presumably because there is no motivation to do so. In other words, it appears that Appellants' hindsight argument is merely a general argument or assertion without substance.

Double Patenting

Argument 1

Appellants argue, "that these [provisional double patenting] rejections be held in abeyance until the remaining issues outstanding in this application have been resolved" citing MPEP § 804.I.B.1 in support of this position that if the non-patenting rejections are the only

rejections remaining in the case that those rejection should be withdrawn without the need for terminal disclaimers (e.g., see 7/6/07 Appeal Brief, pages 25 and 26).

Response 1

The Examiner notes that the double patenting rejections are not the only rejections pending in the present application and, as a result, Appellants' arguments are moot (e.g., see 35 U.S.C. § 103(a) rejection above).

(11) Related Proceedings Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Jon D. Epperson/

Patent Examiner, AU 1639

Conferees:

/J. Douglas Schultz/

Supervisory Patent Examiner, AU 1639

/Ram. R. Shukla/

Supervisory Patent Examiner, AU 1634